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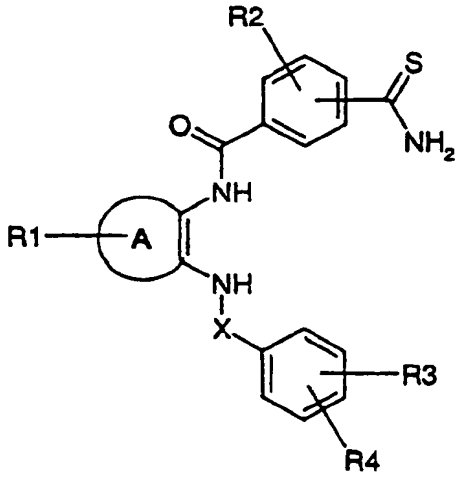
(54) Title: NOVEL THIOBENZAMIDES



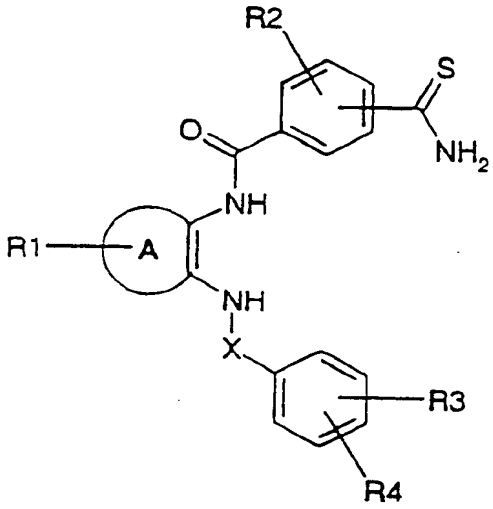
(I)

(57) Abstract

The invention relates to novel thiobenzamides of general formula (I) in which R^1 to R^4 have the meaning indicated in the description, and their hydrates, solvates and physiologically tolerable salts, optically active forms, racemates and diastereomer mixtures, processes for their preparation and medicaments which comprise these compounds, for the treatment of thromboembolic disorders.

Novel thiobenzamides

The invention relates to novel thiobenzamides of the general formula I



(I)

in which

R^1 can be a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a nitro group, a carboxyl group, a carbamoyl group, a thiocarbamoyl group, an alkyl group, a cycloalkyl group, an alkenyl group, an alkynyl group, an alkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an aralkyloxy group, an alkenyloxy group, an alkynyloxy group, a carboxyalkyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, an alkyloxycarbonylalkyl group, an alkenyloxycarbonylalkyl group or an alkynyloxycarbonylalkyl group;

R^2 can be a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a nitro group, a carboxyl group, a carbamoyl group, an alkyl group, a cycloalkyl group, an alkenyl group, an

optically active forms, the racemates and the diastereomer mixtures of these compounds.

The invention also relates to processes for the preparation of the above compounds, medicaments which contain such compounds, and the use of these compounds in the production of medicaments, preferably those with antithromboembolic activity.

Moreover, the invention relates to a method for the prevention and treatment of diseases such as thrombosis, apoplexy, cardiac infarct, inflammations and arteriosclerosis, which comprises the administration of an effective amount of a compound of the formula I.

Further, the invention also relates to pharmaceutical preparations containing at least one compound of the formula I besides conventional carriers and adjuvants.

The thiobenzamides of the general formula I, their solvates and their salts intervene by means of reversible inhibition of factor Xa in the process of blood clotting and thus prevent the formation of hyaline thrombi. They can therefore be used in the control and prevention of diseases, such as thrombosis, apoplexy, cardiac infarct, inflammations and arteriosclerosis.

Factor Xa is a serine protease of the clotting system, which catalyses the proteolytic conversion of prothrombin into thrombin. Thrombin, as the last enzyme in the clotting cascade, on the one hand cleaves fibrinogen to fibrin, which after crosslinking by means of factor XIIIa becomes an insoluble gel and forms the matrix for a thrombus, and on the other hand, by proteolysis of its receptor on the blood platelets, activates platelet aggregation and in this way likewise contributes to thrombus formation. On injury of a blood vessel, these processes are necessary to stop bleeding. Under normal circumstances, measurable thrombin concentrations are not present in the blood plasma. An increase in the thrombin concentration can lead to the

If R^1, R^2 in the general formula I is an alkyl group, this can be straight-chain or branched and can contain 1 to 8 carbon atoms. The methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl, pentyl and the hexyl group are preferred.

If R^1, R^2, R^3, R^4 in the general formula I is a cycloalkyl group, this can be substituted or unsubstituted and can contain 3 to 8 carbon atoms. The cyclopropyl, cyclopentyl, cyclohexyl and the cyclooctyl group are preferred.

If R^1, R^2, R^3, R^4 in the general formula I is an alkenyl group, this can be straight-chain or branched and can contain 2 to 8 carbon atoms. The vinyl, 1-propenyl, 2-propenyl, 2-methyl-2-propenyl, 1-butenyl, 1-pentenyl and the 1-hexenyl group are preferred.

If R^1, R^2, R^3, R^4 in the general formula I is an alkynyl group, this can be straight-chain or branched and can contain 2 to 8 carbon atoms. The ethynyl and propargyl group are preferred.

An alkoxy group as a substituent R^1, R^2, R^3, R^4 in the general formula I contains 1 to 8 carbon atoms and is straight-chain or branched. The methoxy, ethoxy, *n*-propyloxy, *i*-propyloxy, *n*-butyloxy, *i*-butyloxy, *t*-butyloxy, pentyloxy and the hexyloxy group are preferred.

If R^1, R^2, R^3, R^4 in the general formula I is a hydroxyalkyl group, this can be straight-chain or branched and can contain 1 to 8 carbon atoms. The hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl and the hydroxyhexyl group are preferred.

If R^1, R^2, R^3,R^4 in the general formula I is an alkoxyalkyl group, the alkyl radicals concerned are in each case to be understood as meaning straight-chain or branched alkyl chains having 1 to 8 carbon atoms. The methoxymethyl, ethoxymethyl, methoxyethyl and the ethoxyethyl group are preferred.

If R^1, R^2, R^3, R^4 in the general formula I is an aralkyloxy group, this contains a phenyl group linked

propyl and the ethoxycarbonylpropyl group are preferred.

If R^1, R^2, R^3, R^4 in the general formula I is an alkenyloxycarbonylalkyl group, the alkenyl radical is straight-chain or branched having 3 to 8 carbon atoms and the alkyl chain is straight-chain or branched having 1 to 8 carbon atoms. The allyloxycarbonylmethyl, allyloxycarbonylethyl and the allyloxycarbonylpropyl group are preferred.

If R^1, R^2, R^3, R^4 in the general formula I is an alkynyloxycarbonylalkyl group, the alkynyl radical is straight-chain or branched having 3 to 8 carbon atoms and the alkyl chain is straight-chain or branched having 1 to 8 carbon atoms. The propargyloxycarbonylmethyl, propargyloxycarbonylethyl and the propargyloxycarbonylpropyl group are preferred.

If R^1, R^2, R^3, R^4 in the general formula I is an amino group, this can be unsubstituted or alternatively substituted, namely by one or two C_1-C_6-alkyl groups, preferably methyl or ethyl, by one or two C_3-C_8-cycloalkyl groups, preferably cyclopropyl, cyclopentyl, cyclohexyl or cyclooctyl, by one or two C_1-C_6-hydroxyalkyl groups, preferably hydroxyethyl or hydroxypropyl, by one or two C_3-C_6-alkenyl groups, preferably allyl, by one or two C_3-C_6-alkynyl groups, preferably propargyl, or by one or two aralkyl groups, preferably benzyl. The specification (C_1-C_6)-alkyl in each case stands here for a straight-chain or branched alkyl chain having 1 to 6 carbon atoms, (C_3-C_8)-cycloalkyl refers here to a branched or unbranched cycloalkyl group having 3 to 8 carbon atoms and C_3-C_6-alke(y)nyl alternatively denotes a straight-chain or branched alkenyl or alkynyl group having 3 to 6 carbon atoms.

In the general formula I, the substituents R^3 and R^4 can be identical or different.

Halogens as substituents R^3, R^4 can be fluorine, chlorine, bromine and iodine atoms, but preferably chlorine or bromine atoms.

R^1 is a hydrogen atom, a chlorine atom, a hydroxyl group, a carboxyl group, a methyl group, an ethyl group, a *tert*-butyl group, a methoxy group, an ethoxy group, a *tert*-butyloxy group, a benzyloxy group, an allyloxy group, a methoxycarbonyl group, an ethoxycarbonyl group or an allyloxycarbonyl group;

R^2 is a hydrogen atom, a chlorine atom, a hydroxyl group, a carboxyl group, a thiocarbamoyl group, a methyl group, an ethyl group, a *tert*-butyl group, a methoxy group, an ethoxy group, a *tert*-butyloxy group, a benzyloxy group, an allyloxy group, a methoxycarbonyl group, an ethoxycarbonyl group or an allyloxycarbonyl group;

R^3, R^4 are identical or different and are a hydrogen atom, a chlorine atom, a hydroxyl group, a carboxyl group, a thiocarbamoyl group, a methyl group, an ethyl group, a *tert*-butyl group, a methoxy group, an ethoxy group, a *tert*-butyloxy group, a benzyloxy group, an allyloxy group, a methoxycarbonyl group, an ethoxycarbonyl group or an allyloxycarbonyl group or R^3 and R^4, together with the aryl radical to which they are bonded, form a naphthyl radical;

is one of the aromatic fragments phenylene, pyridine-2,3-diyl, pyridine-3,4-diyl, pyridine-5,6-diyl and

X is a carbonyl group or an SO_2 group.

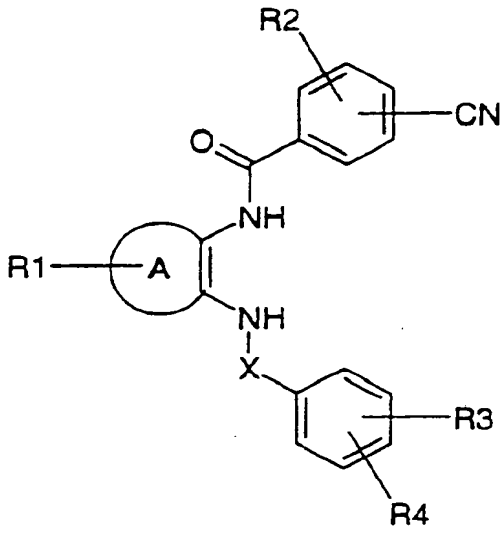
Particularly preferred compounds of the general formula I are those in which R^1 is hydrogen, carboxyl or methoxycarbonyl, R^2 is hydrogen, R^3, R^4 are identical or different and are hydrogen, carboxyl, thiocarbamoyl or methoxy or R^3 and R^4, together with the aryl radical

stration form is preferred. The injection medium used is preferably water, which contains the additives customary in injection solutions such as stabilizing agents, solubilizers or buffers. Additives of this type are, for example, tartrate and citrate buffers, complexing agents (such as ethylenediaminetetraacetic acid and its non-toxic salts) and high molecular weight polymers such as liquid polyethylene oxide for viscosity regulation. Solid excipients are, for example, starch, lactose, mannitol, methylcellulose, talc, highly disperse silicic acids, high molecular weight fatty acids (such as stearic acid), animal and vegetable fats and solid high molecular weight polymers (such as polyethylene glycols). If desired, preparations suitable for oral administration can contain flavourings and sweeteners.

The compounds are customarily administered in amounts of 1-1500 mg per day based on a body weight of 75 kg. It is preferred to administer 1-2 tablets having an active compound content of 1-500 mg 2-3 times per day. The tablets can also be delayed-release, as a result of which only 1-2 tablets containing 2-700 mg of active compound have to be given once per day. The active compound can also be given by injection 1-8 times per day or by continuous infusion, 5-2000 mg per day normally being sufficient.

Compounds of the general formula I are prepared by methods known per se.

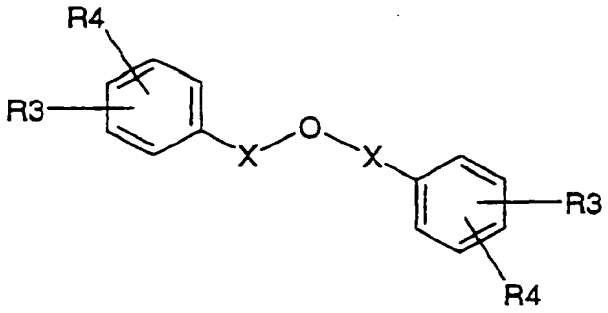
The compounds of the general formula I are prepared, for example, by reacting a compound of the general formula III



(III)

in which R^1, R^2, R^3, R^4, X and  have the significances given above, with hydrogen sulphide in an inert solvent such as, for example pyridine, ethanol methanol or N,N-dimethylformamide at temperatures between 0°C and the boiling point of the solvent, preferably at 0 to 30°C in the presence of an auxiliary base such as, for example, triethylamine, N-methylmorpholine, ethyldiisopropylamine or in the presence of saturated ethanolic ammonia solution. Instead of hydrogen sulphide, other sulphidizing reagents such as ammonium sulphide, sodium sulphide/trimethylchlorosilane, sodium trimethylsilyl sulphide and bis(trimethylsilyl sulphide) can also be employed. If appropriate, the reaction can also be carried out under acidic conditions by using thioacetamide or thiobenzamide as sulphidizing reagents.

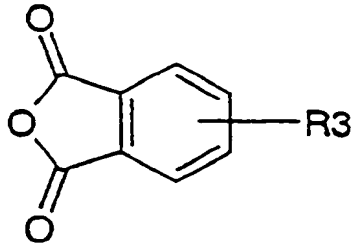
The compounds of the general formula III are prepared by reacting a compound of the general formula IV



(VI)

in which R^3 and R^4 have the meanings indicated above and X is a carbonyl group or an SO_2 group, in an inert solvent such as, for example, pyridine, N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran, dichloromethane or toluene at temperatures between 0°C and the boiling point of the solvent, preferably at 0 to 30°C, if appropriate in the presence of a base such as, for example, sodium carbonate, potassium carbonate, 1,5-diazabicyclo[5.4.0]undec-5-ene, triethylamine, N-methylmorpholine or ethyldiisopropylamine or alternatively in the presence of a catalyst such as, for example, 4-(dimethylamino)-pyridine.

Certain compounds of the general formula III in which R^1, R^2, R^3 and  have the meanings indicated above, R^4 is a carboxyl group and X is a carbonyl group can also be prepared by reacting, for example, a compound of the general formula IV in which R^1, R^2 and  have the meanings indicated above, with a compound of the general formula VII



(VII)

in which R^3 has the meanings indicated above, in an inert solvent such as, for example, pyridine, N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetra-

these compounds can be converted into the corresponding compounds of the general formula III having a free carboxyl group.

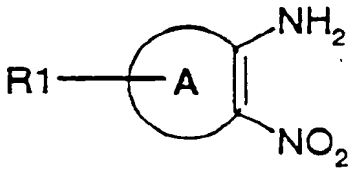
This also relates to compounds of the general formula III in which R^1, R^2, R^3, R^4, X and  have the meanings indicated above, and one or more of the radicals R^1, R^2, R^3, R^4 is a benzyloxy group. By means of catalytic hydrogenation in inert solvents such as, for example, methanol, ethanol, tetrahydrofuran or dioxane in the presence of a catalyst, preferably palladium on carbon, the benzyl group is in this case replaced by a hydrogen atom (see, for example: T.W. Green, P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley and Sons Inc., 1991). The removal of the benzyl group is also carried out by reaction with a strong acid such as trifluoroacetic acid in the presence of mesitylene, anisole or thioanisole at temperatures between 0 and 50°C, preferably at room temperature, or by treatment with Lewis acids such as boron trifluoride etherate in an inert solvent such as toluene, acetonitrile, diethyl ether or tetrahydrofuran at temperatures between 0°C and the boiling point of the solvent, preferably between room temperature and the boiling point of the solvent.

This also relates to compounds of the general formula III in which R^1, R^2, R^3, R^4, X and  have the meanings indicated above, and one or more of the radicals R^1, R^2, R^3, R^4 is an allyloxy group. By means of transition metal-catalysed cleavage, for example in the presence of a rhodium catalyst such as tris-triphenylphosphine-rhodium chloride or of a palladium catalyst such as tetrakis-triphenylphosphine-palladium in an inert solvent such as tetrahydrofuran or dioxane, if appropriate in the presence of a nucleophile such as, for example, diethyl malonate, tributyltin hydride, 5,5-dimethylcyclohexane-1,3-dione or piperidine at temperatures between 0°C and 50°C, preferably at room

alternatively in the presence of a catalyst such as, for example, 4-(dimethylamino)pyridine.

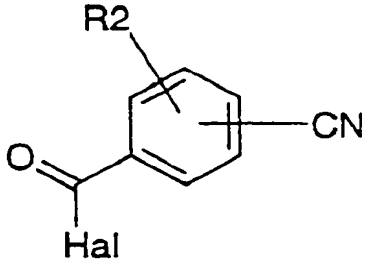
Compounds of the general formulae VIII and IX are either commercially available or are known from the literature or can be prepared according to processes known from the literature.

Compounds of the general formula IV can also be prepared by reacting, for example, a compound of the general formula X



(X)

in which R^1 and  have the meanings indicated above, with a compound of the general formula IX



(IX)

in which R^2 has the meaning indicated above and Hal is a halogen atom, in an inert solvent such as, for example, pyridine, N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran, dichloromethane or toluene at temperatures between 0°C and the boiling point of the solvent, preferably at 0 to 30°C, if appropriate in the presence of a base such as, for example, sodium carbonate, potassium carbonate, 1,5-diazabicyclo[5.4.0]undec-5-ene, triethylamine, N-methylmorpholine or ethyldiisopropylamine or alternatively in the presence of a catalyst such as, for example, 4-(dimethylamino)pyridine and subsequently

temperatures between 0°C and the boiling point of the solvent, preferably between room temperature and 60°C, these compounds can be converted into the corresponding compounds of the general formula I having a free carboxyl group.

This also relates to compounds of the general formula I in which R^1, R^2, R^3, R^4, X and  have the meanings indicated above, and one or more of the radicals R^1, R^2, R^3, R^4 is a benzyloxy group. By means of catalytic hydrogenation in inert solvents such as, for example, methanol, ethanol, tetrahydrofuran or dioxane in the presence of a catalyst, preferably palladium on carbon, the benzyl group is in this case replaced by a hydrogen atom (see, for example: T.W. Green, P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley and Sons Inc., 1991). The removal of the benzyl group is also carried out by reaction with a strong acid such as trifluoroacetic acid in the presence of mesitylene, anisole or thioanisole at temperatures between 0 and 50°C, preferably at room temperature, or by treatment with Lewis acids such as boron trifluoride etherate in an inert solvent such as toluene, acetonitrile, diethyl ether or tetrahydrofuran at temperatures between 0°C and the boiling point of the solvent, preferably between room temperature and the boiling point of the solvent.

This also relates to compounds of the general formula I in which R^1, R^2, R^3, R^4, X and  have the meanings indicated above, and one or more of the radicals R^1, R^2, R^3, R^4 is an allyloxy group. By means of transition metal-catalysed cleavage, for example in the presence of a rhodium catalyst such as tris-triphenylphosphine-rhodium chloride or of a palladium catalyst such as tetrakis-triphenylphosphine-palladium in an inert solvent such as tetrahydrofuran or dioxane, if appropriate in the presence of a nucleophile such as, for example, diethyl malonate, tributyltin hydride,

9. Methyl 6-(3,4-dimethoxybenzoylamino)-5-(4-thiocarbamoylbenzoylamino)nicotinate

10. Methyl 5-(3,4-dimethoxybenzoylamino)-6-(4-thiocarbamoylbenzoylamino)picolinate

11. Methyl 6-(2-carboxybenzoylamino)-5-(4-thiocarbamoylbenzoylamino)nicotinate

12. Methyl 5-(2-carboxybenzoylamino)-6-(4-thiocarbamoylbenzoylamino)picolinate

13. Methyl 6-(4-methoxybenzenesulphonylamino)-5-(4-thiocarbamoylbenzoylamino)nicotinate

14. Methyl 5-(4-methoxybenzenesulphonylamino)-6-(4-thiocarbamoylbenzoylamino)picolinate

15. Methyl 6-(naphthalene-2-sulphonylamino)-5-(4-thiocarbamoylbenzoylamino)nicotinate

16. Methyl 5-(naphthalene-2-sulphonylamino)-6-(4-thiocarbamoylbenzoylamino)picolinate

17. 6-(Naphthalene-2-sulphonylamino)-5-(4-thiocarbamoylbenzoylamino)nicotinic acid

18. 5-(Naphthalene-2-sulphonylamino)-6-(4-thiocarbamoylbenzoylamino)picolinic acid

19. 2,3-Bis(4-thiocarbamoylbenzoylamino)pyridine

20. Methyl 3-[(naphthalene-2-carbonyl)amino]-4-(4-thiocarbamoylbenzoylamino)benzoate

21. 3-[(Naphthalene-2-carbonyl)amino]-4-(4-thiocarbamoylbenzoylamino)benzoic acid

35. 3-(3,4-Dimethoxybenzoylamino)-4-(4-thiocarbamoylbenzoylamino)benzoic acid

36. 4-(3,4-Dimethoxybenzoylamino)-3-(4-thiocarbamoylbenzoylamino)benzoic acid

37. 6-(3,4-Dimethoxybenzoylamino)-5-(4-thiocarbamoylbenzoylamino)nicotinic acid

38. 5-(3,4-Dimethoxybenzoylamino)-6-(4-thiocarbamoylbenzoylamino)picolinic acid

39. 4-(2-Carboxybenzoylamino)-3-(4-thiocarbamoylbenzoylamino)benzoic acid

40. 4-(2,4-Dicarboxybenzoylamino)-3-(4-thiocarbamoylbenzoylamino)benzoic acid

41. 4-(2,5-Dicarboxybenzoylamino)-3-(4-thiocarbamoylbenzoylamino)benzoic acid

42. Methyl 4-(2,4-dicarboxybenzoylamino)-3-(4-thiocarbamoylbenzoylamino)benzoate

43. Methyl 4-(2,5-dicarboxybenzoylamino)-3-(4-thiocarbamoylbenzoylamino)benzoate

44. 4-(4-Methoxybenzenesulphonylamino)-3-(4-thiocarbamoylbenzoylamino)benzoic acid

45. 3-(4-Methoxybenzenesulphonylamino)-4-(4-thiocarbamoylbenzoylamino)benzoic acid

46. Methyl 3-(4-methoxybenzenesulphonylamino)-4-(4-thiocarbamoylbenzoylamino)benzoate

47. 6-(4-Methoxybenzenesulphonylamino)-5-(4-thiocarbamoylbenzoylamino)nicotinic acid

obtained after drying as a white, crystalline solid of m.p. 202-204°C. EI-MS: 295 (M^+).

3. Methyl 4-[(naphthalene-2-carbonyl)amino]-3-(4-cyanobenzoylamino)benzoate

A solution of 1.50 g (0.005 mol) of methyl 4-amino-3-(4-cyanobenzoylamino)benzoate and 10 mg (cat.) of 4-dimethylaminopyridine in 30 ml of abs. pyridine is treated at 5°C with a solution of 1.10 g (0.006 mol) of 2-naphthoyl chloride in 10 ml of abs. pyridine and the mixture is stirred at room temperature for 72 h. It is concentrated, treated with water and ethyl acetate and filtered, the residue is washed successively with water and diethyl ether and 1.65 g (75%) of the title compound are obtained after drying as a white, crystalline solid of m.p. 142°C. EI-MS: 449 (M^+).

4. Methyl 4-[(naphthalene-2-carbonyl)amino]-3-(4-thiocarbamoylbenzoylamino)benzoate

Hydrogen sulphide is passed into a solution of 1.50 g (0.0033 mol) of methyl 4-[(naphthalene-2-carbonyl)amino]-3-(4-cyanobenzoylamino)benzoate and 2.5 ml of triethylamine in 25 ml of abs. pyridine at room temperature until it is saturated. The mixture is stirred at room temperature for 6 h and allowed to stand overnight. The precipitated yellow solid is separated off, washed with water and diethyl ether and dried. Yield: 1.40 g (88%); m.p. 224°C (dec.); EI-MS: 295 (M^+).

2. 2-(4-Methoxybenzoylamino)-1-(4-thiocarbamoyl-benzoylamino)benzene

A solution of 2.37 g (0.010 mol) of 2-(4-cyano-benzoylamino)aniline and 10 mg (cat.) of 4-dimethylaminopyridine in 50 ml of abs. pyridine is treated at 5°C with a solution of 2.05 g (0.012 mol) of 4-methoxybenzoyl chloride in 10 ml of abs. pyridine and the mixture is stirred at room temperature for 16 h. After addition of 10 ml of triethylamine, hydrogen sulphide is passed in at room temperature until the mixture is saturated. It is stirred at room temperature for 6 h, allowed to stand overnight and concentrated, the residue is treated with 50 ml of water and the mixture is extracted twice with 50 ml of ethyl acetate each time. The organic phase is washed with 50 ml of saturated sodium chloride solution, dried and evaporated. The resulting yellow solid is washed with a little diethyl ether and dried. Yield: 3.85 g (95%); m.p. 247°C; (+)-LSI-MS: 406 (MH^+).

Example 4:

Methyl 4-(4-methoxybenzoylamino)-3-(4-thiocarbamoyl-benzoylamino)benzoate

A solution of 0.74 g (0.0025 mol) of methyl 4-amino-3-(4-cyanobenzoylamino)benzoate and 10 mg (cat.) of 4-dimethylaminopyridine in 20 ml of abs. pyridine is treated at 5°C with a solution of 0.51 g (0.0030 mol) of 4-methoxybenzoyl chloride in 5 ml of abs. pyridine and the mixture is stirred at room temperature for 16 h. After addition of 2.5 ml of triethylamine, hydrogen sulphide is passed in at room temperature until the mixture is saturated. It is stirred at room temperature for 6 h, allowed to stand overnight and concentrated. The precipitated yellow solid is

solid is separated off, washed with water and diethyl ether and dried. Yield: 1.00 g (83%); m.p. 288-290°C; (-)-ESI-MS: 476 ($M-H^-$).

Example 7:

Methyl 4-(4-methoxybenzenesulphonylamino)-3-(4-thiocarbamoylbenzoylamino)benzoate

A solution of 0.74 g (0.0025 mol) of methyl 4-amino-3-(4-cyanobenzoylamino)benzoate and 10 mg (cat.) of 4-dimethylaminopyridine in 25 ml of abs. pyridine is treated at 5°C with 1.28 g (0.0063 mol) of 4-methoxybenzenesulphonyl chloride and the mixture is stirred at room temperature for 72 h. After addition of 2.5 ml of triethylamine, hydrogen sulphide is passed in at room temperature until the mixture is saturated. It is stirred at room temperature for 6 h, allowed to stand overnight and concentrated, the residue is treated with 50 ml of water and the mixture is extracted twice with 50 ml each of ethyl acetate. The organic phase is washed with 50 ml of saturated sodium chloride solution, dried and evaporated. The resulting yellow solid is washed with a little diethyl ether and dried. Yield: 0.80 g (67%); m.p. 181°C (dec.); (+)-ESI-MS: 500 (MH^+).

Example 8:

Methyl 4-(naphthalene-2-sulphonylamino)-3-(4-thiocarbamoylbenzoylamino)benzoate

A solution of 0.74 g (0.0025 mol) of methyl 4-amino-3-(4-cyanobenzoylamino)benzoate and 10 mg (cat.) of 4-dimethylaminopyridine in 25 ml of abs. pyridine is treated at 5°C with 1.10 g (0.0050 mol) of naphthalene-2-sulphonyl chloride and the mixture is stirred at room temperature for 16 h. After addition of 2.5 ml of triethylamine, hydrogen sulphide is passed in at room

and dried. Yield: 0.96 g (69%); m.p. 292-294°C; (+)-FAB-MS: 435 (MH^+).

Example 10:

4-(Naphthalene-2-sulphonylamino)-3-(4-thiocarbamoyl-benzoylamino)benzoic acid

A solution of 0.24 ml of boron tribromide (2.5 mmol) in 10 ml of methylene chloride is added dropwise at 5°C to a solution of 260 mg (0.5 mmol) of methyl 4-(naphthalene-2-sulphonylamino)-3-(4-thiocarbamoyl-benzoylamnino)benzoate in 10 ml of methylene chloride. After stirring at room temperature for 16 hours, the reaction solution is treated with ice water. The precipitated orange-coloured solid is separated off, washed with water and diethyl ether and dried. Yield: 120 mg (48%); m.p. 215°C (dec.); (+)-ESI-MS: 528 (MNa^+).

Example 11:

Description of pharmacological test

Obtainment of plasma

Nine parts of fresh blood from healthy donors are mixed with one part of a sodium citrate solution (0.11 mol/l) and centrifuged at about 3000 rpm for 10 minutes at room temperature. The plasma is removed by pipette and can be stored at room temperature for about 8 h.

Activated partial thromboplastin time (APTT)

100 µl of citrate plasma and 100 µl of APTT reagent (Diagnostica Stago/Boehringer Mannheim GmbH; contains lyophilizate cephalin with microcrystalline kieselguhr activator) are

substances in the final volume were 500 µM (TT 500).

Inhibition constants

The kinetic measurements were carried out in 0.1 M phosphate buffer containing 0.2 M saline solution and 0.5% polyethylene glycol 6000 (preparation see below) at pH 7.5 and 25°C in polystyrene semimicro cuvettes in a total volume of 1 ml. The reactions were started by addition of enzyme to preincubated solutions, which either contained dimethyl sulphoxide (control) or solutions of the test substance in DMSO (inhibitor stock solutions: 10 mM in DMSO). The increase in the extinction at 405 nm as a result of the release of 4-nitroaniline from the substrate was monitored photometrically over a period of 12 minutes. Measured values (extinction vs time) were determined at an interval of 20 seconds and these data were stored by computer.

The procedure for the determination of the inhibition constants K_i was as follows: the velocities V_0 (change in extinction per second; measurements without inhibitor) and V_i (change in extinction per second; measurements with inhibitor) were determined by linear regression, only the measuring points at which the substrate concentration decreased by less than 15% being taken into account. K_M and V_{max} were determined from a series of measurements (constant inhibitor concentration, variable substrate concentrations) by non-linear fit to the equation

$$V = \frac{V_{max} \times [S]}{[S] + K_M}$$

ment, 850 µl of phosphate buffer are thermostated (25°C) with 100 µl of substrate [H-(D)-Phe-Pip-Arg-4-nitroaniline dihydrochloride; S-2238; Kabi; substrate concentrations used 100, 50, 30 and 20 µM; K_M 4 µM) and 25 µl of inhibitor solution or 25 µl of DMSO (control) in a photometer. The reaction is started by addition of 25 µl of stock solution.

Trypsin:

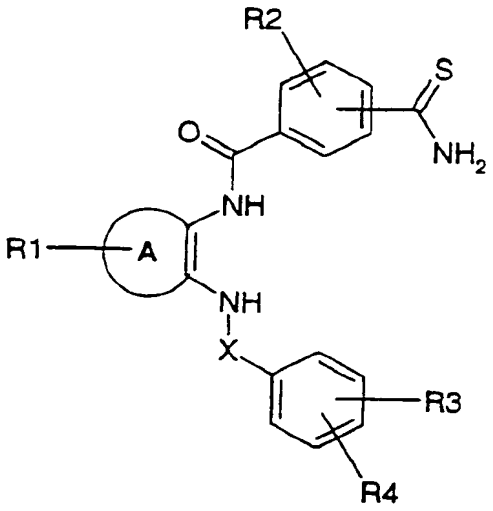
10 mg of bovine pancreatic trypsin (Sigma) are dissolved in 100 ml of 1 mM hydrochloric acid and stored at 2-8°C in a refrigerator. Stock solution: 990 µl of 1 mM hydrochloric acid are treated with 10 µl of the trypsin solution prepared as above and stored on ice for at most 4 hours. For measurement, 850 µl of phosphate buffer are thermostated (25°C) with 100 µl of substrate [H-(D)-Phe-Pip-Arg-4-nitroaniline dihydrochloride; S-2238; Kabi; substrate concentrations used 100, 50, 30 and 20 µM; K_M 45 µM) and 25 µl of inhibitor solution or 25 µl of DMSO (control) in a photometer. The reaction is started by addition of 25 µl of stock solution.

Preparation of the 0.1 M phosphate buffer solution (pH 7.5, 0.2 M NaCl):

8.90 g of $Na_2HPO_4 \cdot 2\ H_2O$, 5.84 g of NaCl and 2.50 g of polyethylene glycol 6000 are dissolved in 400 ml of distilled water and made up to a total volume of 500 ml with distilled water (solution I). 1.36 g of KH_2PO_4, 1.17 g of NaCl and 0.50 g of polyethylene glycol 6000 are dissolved in 80 ml of distilled water and made up to a total volume of 100 ml with distilled water (solution II). Sufficient solution II (about 85 ml) is then added to solution I until the pH is 7.5. The buffer solution is always freshly prepared (can be

Claims

1. Compounds of the general formula I



(I)

in which

R^1 can be a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a nitro group, a carboxyl group, a carbamoyl group, a thiocarbamoyl group, an alkyl group, a cycloalkyl group, an alkenyl group, an alkynyl group, an alkoxy group, a hydroxyalkyl group, an alkoxyalkyl group, an aralkyloxy group, an alkenyloxy group, an alkynyloxy group, a carboxyalkyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, an alkyloxycarbonylalkyl group, an alkenyloxycarbonylalkyl group or an alkynyloxy-carbonylalkyl;

R^2 can be a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, a nitro group, a carboxyl group, a carbamoyl group, an alkyl group, a cycloalkyl group, an alkenyl group, an alkynyl group, an alkoxy group, a hydroxyalkyl

2. Compounds according to claim 1, in which

R^1 is a hydrogen atom, a chlorine atom, a hydroxyl group, a carboxyl group, a methyl group, an ethyl group, a *tert.*-butyl group, a methoxy group, an ethoxy group, a *tert.*-butyloxy group, a benzyloxy group, an allyloxy group, a methoxycarbonyl group, an ethoxycarbonyl group or an allyloxycarbonyl group;

R^2 is a hydrogen atom, a chlorine atom, a hydroxyl group, a carboxyl group, a thiocarbamoyl group, a methyl group, an ethyl group, a *tert.*-butyl group, a methoxy group, an ethoxy group, a *tert.*-butyloxy group, a benzyloxy group, an allyloxy group, a methoxycarbonyl group, an ethoxycarbonyl group or an allyloxycarbonyl group;

R^3, R^4 are identical or different and are a hydrogen atom, a chlorine atom, a hydroxyl group, a carboxyl group, a thiocarbamoyl group, a methyl group, an ethyl group, a *tert.*-butyl group, a methoxy group, an ethoxy group, a *tert.*-butyloxy group, ae benzyloxy group, an allyloxy group, a methoxycarbonyl group, an ethoxy-carbonyl group or an allyloxycarbonyl group or R^3 and R^4, together with the aryl radical to which they are bonded, form a naphthyl radical;

is one of the aromatic fragments phenylene, pyridine-2,3-diyl, pyridine-3,4-diyl and pyridine-5,6-diyl and

X is a carbonyl group or an SO_2 group.

3. The compounds according to claim 1, selected from

methyl 6-[(naphthalene-2-carbonyl)-amino]-5-(4-thiocarbamoyl-benzoylamino)-nicotinate,

5-(naphthalene-2-sulphonylamino)-6-(4-thiocarbamoyl-benzoylamino)-picolinic acid,

2,3-bis-(4-thiocarbamoyl-benzoylamino)-pyridine,

methyl 3-[(naphthalene-2-carbonyl)-amino]-4-(4-thiocarbamoyl-benzoylamino)-benzoate,

3-[(naphthalene-2-carbonyl)-amino]-4-(4-thiocarbamoyl-benzoylamino)-benzoate,

4-(4-methoxy-benzoylamino)-3-(4-thiocarbamoyl-benzoylamino)-pyridine,

3-(4-methoxy-benzoylamino)-4-(4-thiocarbamoyl-benzoylamino)-pyridine,

4-(3,4-dimethoxy-benzoylamino)-3-(4-thiocarbamoyl-benzoylamino)-pyridine,

3-(3,4-dimethoxy-benzoylamino)-4-(4-thiocarbamoyl-benzoylamino)-pyridine,

3-(3,4-dimethoxy-benzoylamino)-2-(4-thiocarbamoyl-benzoylamino)-pyridine,

2-(3,4-dimethoxy-benzoylamino)-3-(4-thiocarbamoyl-benzoylamino)-pyridine,

2-(3,4-dimethoxy-benzoylamino)-1-(4-thiocarbamoyl-benzoylamino)-benzene,

6-(4-methoxy-benzoylamino)-5-(4-thiocarbamoyl-benzoylamino)-nicotinic acid,

5-(4-methoxy-benzoylamino)-6-(4-thiocarbamoyl-benzoylamino)-picolinic acid,

methyl 3-(4-methoxy-benzoylamino)-4-(4-thiocarbamoyl-benzoylamino)-benzoate,

3-(4-methoxy-benzoylamino)-4-(4-thiocarbamoyl-benzoylamino)-benzoic acid,

4-(4-methoxy-benzoylamino)-3-(4-thiocarbamoyl-benzoylamino)-benzoic acid,

methyl 3-(naphthalene-2-sulphonylamino)-4-(4-thiocarbamoyl-benzoylamino)-benzoate,

3-(naphthalene-2-sulphonylamino)-4-(4-thiocarbamoyl-benzoylamino)-benzoic acid,

methyl 4-[(naphthalene-2-carbonyl)-amino]-3-(4-thiocarbamoyl-benzoylamino)-benzoate,

4-[(naphthalene-2-carbonyl)-amino]-3-(4-thiocarbamoyl-benzoylamino)-benzoic acid,

2-(4-methoxy-benzoylamino)-1-(4-thiocarbamoyl-benzoylamino)-benzene,

methyl 4-(4-methoxy-benzoylamino)-3-(4-thiocarbamoyl-benzoylamino)-benzoate,

methyl 4-(3,4-dimethoxy-benzoylamino)-3-(4-thiocarbamoyl-benzoylamino)-benzoate,

methyl 4-(2-carboxy-benzoylamino)-3-(4-thiocarbamoyl-benzoylamino)-benzoate,

methyl 4-(4-methoxy-benzenesulphonylamino)-3-(4-thiocarbamoyl-benzoylamino)-benzoate,

methyl 4-(naphthalene-2-sulphonylamino)-3-(4-thiocarbamoyl-benzoylamino)-benzoate,

1,2-bis-(4-thiocarbamoyl-benzoylamino)-benzene and 4-(naphthalene-2-sulphonylamino)-3-(4-thiocarbamoyl-benzoylamino)-benzoic acid.

4. Compounds according to any one of claims 1-3 for the prevention and treatment of diseases such as thrombosis, apoplexy, cardiac infarct, inflammations and arteriosclerosis.

5. A pharmaceutical composition containing at least one compound according to any one of claims 1-3 in addition to customary carriers and adjuvants.

9. Process according to claim 8, wherein pyridine, ethanol, methanol or N,N-dimethylformamide is used as the solvent.

10. Process according to claim 8 or claim 9, wherein the adjuvant base used in the reaction set forth under a) is triethylamine, N-methylmorpholine or ethyldiisopropylamine.

11. Process according to any one of claims 8-10, wherein hydrogen sulphide, amm0onium sulphide, sodium sulphide/trimethylchlorosilane, sodium trimethylsilyl sulphide or bis-trimethylsilyl sulphide is used as the sulphidizing reagent in the reactiond set forth under a) and/or b).

12. The compounds according to any one of claims 1-3, when prepared according to a process as set forth in any one of claims 8 to 11.

13. The compounds, uses, methods and processes as described above.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/00965

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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..Information on patent family members

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